Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

PLCB2 (phospholipase C, beta 2)

Valeria Bertagnolo, Federica Brugnoli, Mascia Benedusi, Silvano Capitani

Signal Transduction Unit, Laboratory of Cell Biology, Section of Human Anatomy, Department of Morphology and Embryology, University of Ferrara, Ferrara, Italy

Published in Atlas Database: May 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/PLCB2ID41743ch15q15.html
DOI: 10.4267/2042/16958

Identity

Hugo: PLCB2
Other names: FLJ38135
Location: 15q15

DNA/RNA

Note: 32 exons; DNA size 19,93 kb.

Transcription

mRNA size 4518 bp. Two alternatively spliced forms of PLC-b2 have been identified: PLC-b2a and PLC-b2b.
The sequence of PLC-b2a consists of 1181 amino acids (molecular weight 133.7 kDa). PLC-b2b transcript lacks 45 nucleotides in the carboxyl-terminal region and the two splice variants differ by 15 amino acid residues, corresponding to aa 864-878.

Pseudogene

No known pseudogenes.

Protein

Description

The sequence of PLC-b2 contains a PH-domain in the amino-terminal region, that binds to polyhosphoinositides and to cytoskeleton proteins. The catalytic site corresponds to the X and Y domains, highly conserved among PLCs. A C2 domain, present in numerous signaling molecules, is involved in the calcium binding. The long carboxyl-terminal region, located downstream to the C2 domain, is involved in the Gaq mediated activation of the catalytic domains and contains a nuclear localization signal. Additional EF domains are located between the PH and X regions and seem to simply constitute a flexible linker to the X-Y domain.

Expression

PLC-b2, first isolated from a HL-60 cDNA library, is expressed predominantly in cells of haematopoietic origin. The amount of PLC-b2 correlates with the functional maturation of differentiating cells. In platelets, leukocytes and erythroleukemia cells, both the two alternatively spliced forms are present.
PLC-b2 is weakly expressed in breast epithelial cells and shows high levels in tumoral mammary tissues. PLC-b2 was also identified in ATP-secreting taste bud cells.

Localisation

PLC-b2 has both a cytoplasmic and a nuclear localization. In particular, PLC-b2 accumulates inside the nuclear compartment during agonist-induced granulocytic differentiation of tumoral myeloid precursors.
In platelets, expressing both splicing variants, PLC-b2a is most abundant in the nuclear compartment. By means of immunocytochemical analysis, it has been demonstrated that in promyelocytes differentiating

PH: pleckstrin homology domain
EF: EF-hand domain
X and Y: catalytic domains
C2: calcium-binding domain

along the neutrophil lineage, PLC-b2 distribution evokes the spatial organization of the cytoskeleton.

Function

PLC-b2 catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) generating the second messenger molecules inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).
In hematopoietic cells, PLC-b2 plays a crucial role in platelet activation and in response of neutrophils to chemoattractants.
During maturation of tumoral myeloid precursors, it has been demonstrated that the phosphodiesterase activity of PLC-b2 on the actin-associated PIP2 may be responsible, by modifying the phosphoinositide pools, for the modifications of cytoskeleton architecture that take place during motility of differentiating promyelocytes.
In taste bud cells, PLC-b2 is a marker of early differentiation and functional taste signalling.

Homology

PLC-b2 is related to PLC-b1 with an amino acid sequence identity of 48%.

Implicated in

Acute Promyelocytic Leukaemia (APL)

Note: This hematopoietic disorder is a M3 subtype of acute myeloblastic leukemia and is characterized by a block of granulocytopoiesis at the promyelocytic stage. APL blasts present a balanced reciprocal t(15;17) chromosomal translocation encoding the PML / RARA fusion protein that plays a key role in the pathogenesis of the disease.

Disease

PLC-b2, highly present in neutrophils of peripheral blood, is weakly expressed in blasts purified from patients with APL and in APL-derived cell lines.

Prognosis

PLC-b2 shows a large increase of expression during ATRA (all-trans-retinoic acid) and/or As2O3-induced granulocytic differentiation of both APL-derived cell lines and blasts purified from patients with APL. PLC-b2 expression during differentiating treatments correlates with the granulocytic maturation levels reached by myeloid precursors. In addition, the level of PLC-b2 after ex-vivo ATRA treatment of APL blasts strikingly correlates with the responsiveness of APL patients to ATRA-based therapies.
This evidence demonstrates that PLC-b2 represents a specific marker for monitoring the agonist-induced overcoming of the maturation blockade of tumoral promyelocytes.

Oncogenesis

It has been reported that co-repressors bound to PML-RARa are released from DNA upon both ATRA and As2O3-treatment of APL cells leading to the activation of genes repressed by the fusion protein. This suggests that the reduced expression of PLC-b2, whose gene is located on chromosome 15, which is involved in the (15;17) translocation, may be related to the presence of the fusion protein. The increased expression of PLC-b2, induced by both ATRA and As2O3, may be related indeed to the removal of the fusion protein, that seems to constitute a common step of the differentiation pathways activated by the two agonists.

Breast cancer

Note: Breast cancer is highly heterogeneous and, during its sequential in vivo progression from atypical hyperproliferation to metastatic disease, tumor cells undergo phenotype alterations, including the loss, to a variable extent, of epithelial-like features, and the gain of more aggressive and invasive mesenchymal-like traits. Like most human neoplasm, breast cancer has aberrations in signal transduction elements that can lead to increased proliferative potential, sustained angiogenesis, apoptosis inhibition and tissue invasion and metastasis. The portrait of breast tumors remains stable during progression and no major changes appear to explain why a tumor may evolve to the metastatic stage and, at present, no marker has been clearly associated with the progression from in situ to invasiveness.

Disease

It has recently been demonstrated, by means of immunohistochemical analysis on tissue microarrays composed of breast cancer specimens and normal epithelia, that PLC-b2, poorly expressed in normal tissues, is up-regulated in almost all tumor cells. In particular, the amount of PLC-b2 correlates with morphological features of the different primary cancers, since weak expression is showed by tumors that retain a differentiated appearance, while a progressively higher amount of protein was revealed in poorly differentiated and undifferentiated tumors.

Prognosis

By analyzing the relationship between PLC-b2 levels and biological and clinic-pathological factors, it has been found that the expression of PLC-b2 strikingly correlates with histological grade, mitotic index and size of primary tumors. No differences in PLC-b2 amount were found in breast tumors that express estrogens and/or progesterone receptors, while tumors negative for at least one of the two receptors showed elevated expression of this enzyme, as well as the majority of HER-2 positive tumours. These data suggest that high amounts of PLC-b2 might be associated to a worse response to therapy.
Survival analysis of cancer-related death indicates that patients whose primary tumors express low levels of PLC-b2 show an overall survival significantly higher in comparison to patients whose primary tumors express

high levels of protein. In addition, elevated PLC-b2 expression of primary breast cancer is associated with a shorter relapse-free time interval.

References

Park D, Jhon DY, Kriz R, Knopf J, Rhee SG. Cloning, sequencing, expression, and Gq-independent activation of phospholipase C-beta-2. J Biol Chem 1992;267:16048-16055.

Bertagnolo V, Marchisio M, Capitani S, Neri LM. Intranuclear translocation of phospholipase C beta2 during HL-60 myeloid differentiation. Biochem Biophys Res Commun 1997;235:831-835.

Li Z, Jiang H, Xie W, Zhang Z, Smrcka AV, Wu D. Roles of PLC-beta-2 and -beta-3 and PI3K-gamma in chemoattractant-mediated signal transduction. Science 2000;287:1046-1049.

Rebecchi MJ, Pentyala SN. Structure, function, and control of phosphoinositide-specific phospholipase C. Physiol Rev 2000;80:1291-1335.

Bertagnolo V, Marchisio M, Pierpaoli S, Colamussi ML, Brugnoli F, Visani G, Zauli G, Capitani S. Selective up-regulation of phospholipase C-beta2 during granulocytic differentiation of normal and leukemic hematopoietic progenitors. J Leukoc Biol 2002;71:957-965.

Bertagnolo V, Benedusi M, Querzoli P, Pedriali M, Magri E, Brugnoli F, Capitani S. PLC-beta2 is highly expressed in breast cancer and is associated with a poor outcome: a study on tissue microarrays. Int J Oncol 2006;28:863-872.

Brugnoli F, Bovolenta M, Benedusi M, Miscia S, Capitani S, Bertagnolo V. PLC-beta2 monitors the drug-induced release of differentiation blockade in tumoral myeloid precursors. J Cell Biochem 2006;98:160-173.

Hamamici R, Asano-Myyoshi M, Emori Y. Taste bud contains both short-lived and long-lived cell populations. Neuroscience 2006;141:2129-2138.

Bertagnolo V, Benedusi M, Brugnoli F, Lanuti P, Marchisio M, Querzoli P, Capitani S. Phospholipase C-beta2 promotes mitosis and migration of human breast cancer derived cells. Carcinogenesis 2007;Epub ahead of print.

Brugnoli F, Bavelloni A, Benedusi M, Capitani S, Bertagnolo V. PLC-beta2 activity on actin associated polyphosphoinositides promotes migration of differentiating tumoral myeloid precursors. Cell Signal 2007;Epub ahead of print.

Sun L, Mao G, Kunapuli SP, Dhanasekaran DN, Rao AK. Alternative splice variants of phospholipase C-beta2 are expressed in platelets: effects on Galphaq-dependent activation and localization. Platelets 2007;18:217-223.

This article should be referenced as such:
Bertagnolo V, Brugnoli F, Benedusi M, Capitani S. PLCB2 (phospholipase C, beta 2). Atlas Genet Cytogenet Oncol Haematol.2007;11(4):308-310.